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EFFECT OF DIETARY ENERGY INTAKE AND EXOGENOUS PORCINE GROWTH HORMONE ADMINISTRATION ON CIRCULATING PORCINE GROWTH HORMONE CONCENTRATION AND RESPONSE TO HUMAN GROWTH HORMONE–RELEASING FACTOR ADMINISTRATION IN GROWING SWINE[1,2]

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ABSTRACT

In a 2 × 2 treatment array (n = 4 pigs/treatment), the effects of feed intake (ad libitum vs. restricted to 60% ad libitum) and the daily administration of excipient buffer or porcine pituitary-derived growth hormone (GH) at a dose of 100 μg/kg body weight per day on serum GH profile and human growth hormone–releasing factor (hGRF) response were examined in barrows weighing 55 kg. Feed intake treatment was implemented from 25 to 55 kg live weight. Buffer or GH treatment was implemented for 10 d before sampling. After GH treatment, the integrated serum GH concentration area was 25% greater in barrows fed restrictively. Data are consistent with the suggestion that GH dose to improve the efficiency of lean tissue deposition be adjusted according to feeding regimen. The serum GH response to hGRF was also altered by level of feed intake. The ad libitum feeding of buffer-treated animals resulted in a monophasic serum GH response to hGRF, whereas barrows fed restrictively had a biphasic response to hGRF. Together, these data suggest that feed intake pattern alters GH secretion and as such could influence the practical implementation of somatotropin as a metabolism modifier in swine.

INTRODUCTION

The treatment of both young, growing (<60 kg) and older, finishing (>60 kg) swine with exogenous pituitary-derived growth hormone (GH) or porcine somatotropin (PST), the recombinantly derived mimic, markedly improves growth performance and carcass characteristics by enhancing the partition of nutrients toward lean tissue accretion (1–6). Likewise, the restriction of energy intake reduces carcass fat content and reduces the fat:lean ratio (7). The effects of porcine GH (pGH) administration on growth performance and protein and energy metabolism are largely independent of, and additive to, the effects of dietary energy intake (3,4).

The hypothesis of this study was that feed intake pattern influences GH metabolism. Therefore, the objectives were: 1) to determine the effect of dietary energy intake, synonymous with feed intake, on the temporal circulating GH concentration of control and GH-treated pigs and 2) to examine the effects of dietary energy and GH treatment on the responsiveness of the pituitary gland to a GH secretagogue.

MATERIALS AND METHODS

As a companion trial to that described by Campbell et al. (3), Durox × Yorkshire barrows were fed ad libitum from weaning until they achieved 25 kg live weight, at which

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time, animals were individually penned with free access to water. Eight barrows were fed ad libitum the diet as described previously (3), whereas eight additional barrows were similarly managed but restricted to 60% of ad libitum intake calculated according to the Agricultural Research Council (ARC) (8; MegaJoule digestible energy = $0.60 \times 55 [1 - e^{-0.0204 \times \text{body weight, kg}}]$). Ad libitum intake was calculated by use of the prior guideline, and animals were trained to consume the calculated daily allowance between 0800 and 1200 hr. The implementation of dietary treatment was staggered such that all barrows achieved 55 kg live weight at approximately the same time. Ten days before the achievement of 55 kg live weight, four pigs within each dietary treatment group were injected daily with excipient diluent (50 mM carbonate-bicarbonate buffer in 0.15 M NaCl, pH 9.4) into the extensor musculature of the neck and the remaining four barrows were injected with GH at a dose of 100 μg/kg body weight per day. Solutions of GH were prepared daily, immediately before use. Animals were weighed every third day, and feed allowance and GH dose were adjusted correspondingly.

At 55 kg, pigs were surgically fitted with vena cava catheters as described by Brocht et al. (9). On Study Day 1 (episodic), 49 blood samples (5 ml) for serum harvest were collected from each pig before and after GH treatment and feeding over the period from 0600 to 1800 hr. On Study Day 2 (human growth hormone releasing factor; hGRF at 10 μg/kg body weight), blood samples were collected before and after feeding and treatment with hGRF. A total of 24 samples were collected from each pig between 0700 and 1230 hr. Specific sampling frequencies and arbitrary sampling designations for each study day are defined in Table 1.

Serum was stored at −20° C before analysis. The circulating GH concentration was determined by radioimmunoassay as described previously (10). Briefly, within-assay variation was <10%, and intra-assay variation was 12.7% with a sensitivity of 0.05 ng/tube. Baseline nadir (average mean baseline) is the mean of fasting concentrations on each day, which was then subtracted from subsequent datum points. Data from both study days were evaluated by use of the PC-PULSAR version 1.3A (11) to determine secretory frequency, amplitude of secretory spikes, and integrated serum GH response area for each animal. Treatment main effects for GH administration and dietary energy intake were

TABLE 1. SAMPLING PROTOCOL FOR THE EFFECT OF GH ADMINISTRATION AND FEED INTAKE ON SERUM GH PROFILES OF BARROWS AT 55 KG LIVE WEIGHT

Study Day	Time	Interval Designation[a]
1 (episodic)		
	0600–0800	Fasting (n = 9)[b]
	0815	Sample, feed and inject with buffer or GH
	0830–0930	Postfeeding (n = 5)
	0945–1300	Postprandial (n = 14)
	1315–1800	Postabsorptive (n = 20)
2 (GRF)[c]		
	0700–0745	Fasting (n = 4)
	0800	Sample and feed
	0810–0920	Postfeeding (n = 8)
	0930	Sample and infuse with GRF[d]
	0935–1230	Postprandial/post-hGRF (n = 10)

[a] Blood samples were collected at 15-min intervals on Study Day 1. On Study Day 2, samples were collected at 15-min intervals before feeding, at 10-min intervals after feeding, and at 5, 10, 20, 30, 45, 60, 75, 90, 120, and 180 min after hGRF infusion.
[b] n designates the number of blood samples per animal collected at each interval.
[c] All animals fed restrictively.
[d] hGRF, 1-44 was purchased from Bachem, Inc., Budendorf, Switzerland, and was infused intravenously at a dose of 10 μg/kg body weight.

evaluated by use of the General Linear Model analysis of variance procedure of SAS (12) and were noted as significant at the $P < 0.05$ level of probability.

RESULTS

Data from Study Days 1 (episodic) and 2 (hGRF) are summarized in Table 2. Additionally, individual treatment mean data for each sampling time are shown in Figure 1A (episodic) and 1B (hGRF).

Twenty-four hours after GH treatment, the baseline circulating GH concentration tended to be reduced ($P < 0.06$) in GH-treated as compared with excipient-treated barrows. The number of pGH peaks was reduced ($P < 0.05$) by GH treatment. The peak GH amplitude (in nanograms per milliliter) was reduced in ad libitum-fed, GH-treated barrows compared with that in counterparts fed restrictively, resulting in a significant ($P < 0.05$) intake × GH interaction. This effect of intake on peak amplitude persisted over the entire sampling period, resulting in a significant ($P < 0.05$) intake × GH interaction for integrated response area. Energy level had no effect on baseline GH concentration or on the frequency of GH peaks, nor was the interaction of intake and GH treatment significant.

The following day (Study Day 2), animals were sampled for a 90-min period before and after feeding. hGRF was administered as a bolus infusion 90 min after feeding at a dose of 10 μg/kg body wt dissolved in 10 ml of saline. Neither basal GH concentration nor secretory peak frequency was influenced by GH or intake. The pituitary responsiveness to hGRF, evaluated from peak amplitude data, was ablated by prior treatment with GH. Control pigs fed ad libitum and treated with hGRF responded with a greater increase in circulating GH as compared with counterparts fed restrictively, resulting in a significant ($P < 0.05$) intake × GH interaction. However, the integrated response area revealed no effect of intake pattern. This can be attributed to a delayed and apparently biphasic release of GH after the hGRF challenge of pigs fed restrictively (Figure 1B).

TABLE 2. EFFECT OF PGH (GH) ADMINISTRATION AND DIETARY ENERGY INTAKE (EI) ON CIRCULATING GH PROFILES OF GROWING PIGS[a]

	Feeding Level of pGH (g/kg body weight per day)					
	Ad Libitum		60% Ad Libitum			
Study Day Item	0	100	0	100	SE[b]	Analysis of Variance
Day 1 (episodic)						
Baseline mean (nadir) GH (ng/ml)	2.58	0.73	1.77	1.29	0.55	NS
Secretory peaks (n)	8.00	4.25	9.50	3.50	1.18	GH
Peak GH amplitude (ng/ml)	3.26	18.85	1.98	28.42	2.36	GH, GH × EI
Area under curve (ng/min per ml)	267	5612	235	7830	501	GH, EI, GH × EI
Day 2 (hGRF)						
Baseline mean (nadir) GH (ng/ml)	2.31	0.64	1.35	1.06	0.49	NS
Secretory peaks (n)	1.25	2.00	2.00	2.00	0.31	NS
Peak GH amplitude (ng/ml)	9.77	1.36	4.99	1.47	1.07	GH, EI, GH × EI
Area under curve (ng/min per ml)	321	46	400	36	99	GH

[a] Blood samples were taken from barrows at 55 kg live weight at the times designated in Table 1.
[b] Pooled standard error (SE) with four animals per treatment cell.
[c] Significant effect ($P < 0.05$) of energy intake (EI), pGH (GH), or the EI × GH interaction.
NS designates no treatment effects.

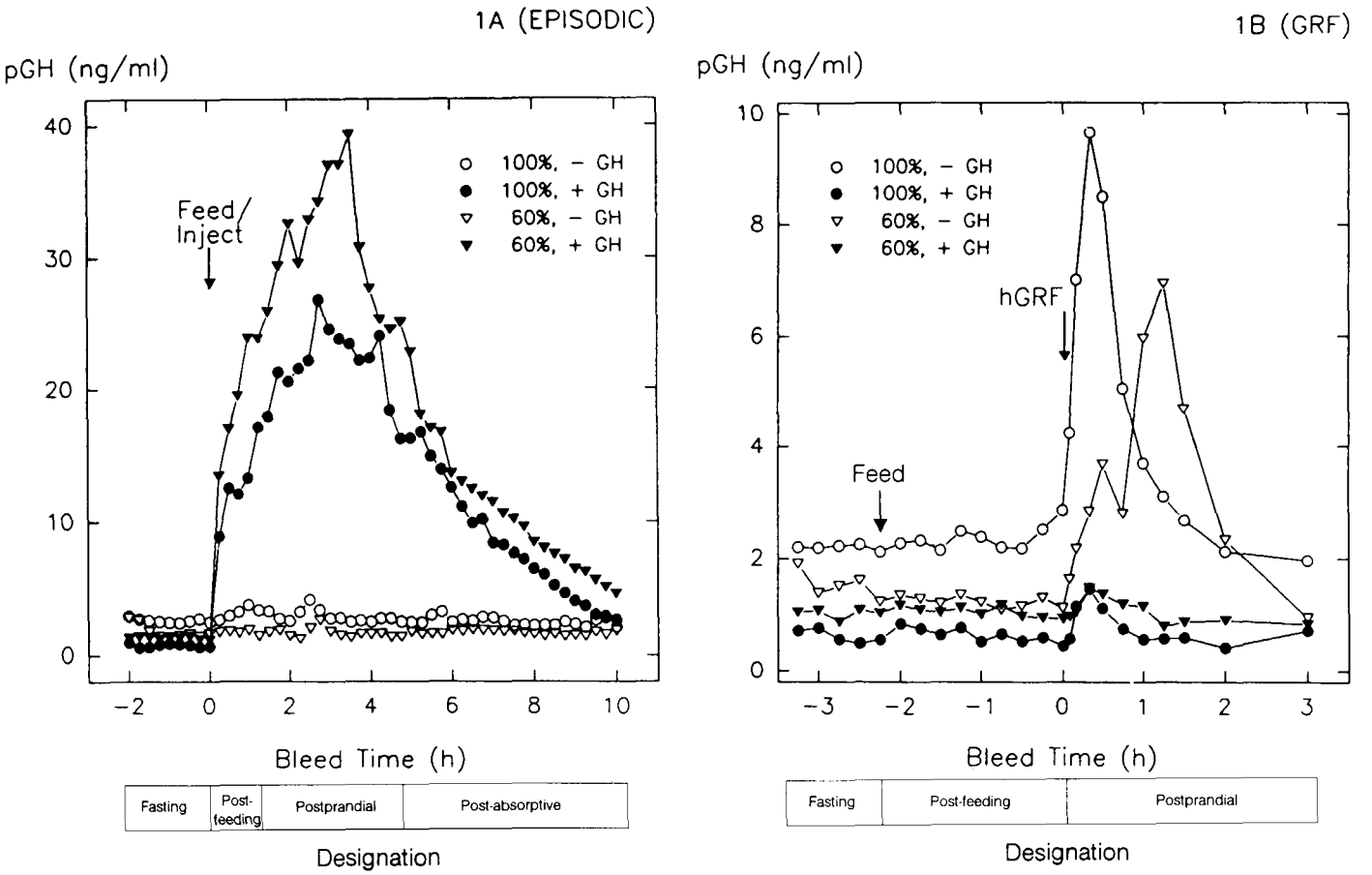

Figure 1. (A) (Episodic). Effect of treatment of barrows with excipient buffer or pGH on serum GH concentration before and after ad libitum or restrictive feeding of a common diet. Each point represents the mean of four animals sampled as described in Table 1. (B) (hGRF). Serum GH profile of barrows previously treated with excipient buffer or pGH and fed ad libitum or restrictively a common diet followed by infusion with hGRF. Each point represents the mean of four animals sampled as described in Table 1.

DISCUSSION

As reported by Campbell et al. (3), the treatment of pigs with GH will benefit the efficiency of lean tissue deposition whether animals are fed ad libitum or on a restricted basis, but maximum benefit could be expected under conditions where energy intake is not limited. Furthermore, plotting energy retention as protein and fat components of the carcass suggested that dietary energy intake and GH treatment affect the fat:lean ratio of the carcass by independent and additive mechanisms. As in the study reported by Campbell et al. (3), Johnson et al. (13) reported a reduction in voluntary feed intake (10%) as a result of chronic somatotropin treatment. The depression of appetite attributable to GH/PST treatment is a function of body weight and is more severe during the finishing period (>60 kg) of growth (14). Because of the abbreviated GH treatment duration (10 d) of ad libitum–fed, grower-phase (<55 kg) barrows, no discernible reduction of feed intake was noted in this study. All barrows treated with GH were hyperinsulinemic, a consistent GH response (1–5).

The hypothesis of this study was that feeding strategy per se influenced GH metabolism and could affect the utility of GH/PST use. Solely on the basis of the temporal circulating GH profile in pigs of identical live weight, genetic background, and pretreatment management, the practical implementation of GH administration will differ depending on feeding strategy. Data are consistent with the suggestion that the maximum biologic response of restrictively fed pigs to GH, i.e., the accretion rate of lean tissue, could be realized with approximately 25% less GH administered on a body weight basis. This rationale assumes that maximum benefit would occur with a daily injection, or surge, delivery method, which achieved a peak circulating concentration of approximately >20 to 30 ng of GH per milliliter.

Krick et al. (15) reported that average daily gain and protein accretion were dose responsive to PST in ad libitum–fed pigs, with a maximum occurring at approximately 100 μg/kg body weight per day. Other growth performance parameters, specifically, lipid accretion rate, have characteristic dose maximums; however, feed intake confounds the interpretation of data because voluntary intake decreased linearly over the range of PST doses examined. This study attempted to characterize intake per se as a factor affecting the metabolism of GH. On the basis of the circulating concentration, restrictive feeding alters GH secretion and as such the dose-response relationships affecting growth performance traits will be altered. Restrictive feeding does not effect pituitary gland GH concentration (3), but unknown are the effects of food intake on the volume of distribution and(or) the metabolic clearance rate of exogenously administered GH. The practical implication is that those production environments not using ad libitum feeding conditions will likely optimize response with a lower dosage of GH administration.

Prior treatment of pigs with GH, even for a short period of time, negates the stimulation of GH release by the pituitary gland in response to hGRF administration. Previously, we reported a sustained benefit in growth performance long after the cessation of GH treatment (16). This suggests that the normal physiologic control of endogenous GH secretion is ultimately restored after the cessation of GH treatment. Feeding regimen had little effect on the pituitary gland response to hGRF; albeit, restricted feeding reduced the amplitude of the secretory surge, but the pattern shifted from monophasic to biphasic.

In summary, the pattern of feed intake, ad libitum or restricted to 60% of ad libitum intake, alters the profile of serum GH concentration in barrows after the administration of 100 μg of pGH/kg body weight per day. The feeding regimen also alters the serum GH profile of barrows treated with excipient buffer and hGRF. Data suggest that feed man-

agement practice must be considered in the determination of the efficacious pGH or PST dosing of pigs to improve the efficiency of lean tissue deposition.

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[2] Mention of a trade name or proprietary product does not constitute an endorsement or an implied warranty by the U.S. Department of Agriculture to the exclusion of other products or vendors that might be equally suited.

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